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HEMOPTYSIS AND HEMATURIA IN SPRUE

Importance of Vitamin K Metabolism

Report of a Case

E. N. COLLINS, M.D. and A. D. HOFFMANN, M.D.

Sprue (idiopathic steatorrhea, celiac disease, Gee-Herter disease) is not commonly encountered in nontropical regions. Sprue is considered a chronic deficiency state related to pernicious anemia and to deficient absorption of the erythrocyte-maturing factor, as well as to deficient absorption of fat-soluble substances. Hemoptysis and hematuria are rare complications. The case to be reported not only illustrates the lack of *absorption* of fat-soluble substances, including fat-soluble vitamins, particularly vitamin K, but also may illustrate deficient *synthesis* of vitamin K as a result of the use of succinylsulfathiazole,* which changes the bacterial flora in the intestinal tract.

In this instance the diagnosis of sprue was not established until the second period of observation. Until then the patient had been treated for indeterminate diarrhea. Three years previously an attack of prolonged diarrhea had promptly subsided upon sulfathiazole therapy, which suggested that bacillary dysentery might have been present. Nine days following our initial observation, the patient was readmitted to the hospital as an emergency case with hemoptysis and hematuria.

CASE REPORT

A married white man, aged 31, a storekeeper by occupation, was referred by Dr. J. T. Ledman of Lakewood, Ohio to Dr. J. W. Thomas for allergic investigation. The patient complained of lower abdominal cramplike pain, persistent diarrhea, weakness, and loss in weight.

During the previous 4 months he had had as many as 9 stools daily without observing blood. He had lost 20 pounds in weight. A similar condition 3 years previously had lasted 8 months. Sulfathiazole had been given for 2 weeks and had been followed by a remission of symptoms until the onset of the present attack. The patient had never been in the tropics or Southern states. Dr. Ledman stated that during the present illness stool examination and roentgen examination of the colon had revealed no evidence of an inflammatory process, and there had been no response to the use of sulfathiazole. Even though the patient had never had hay fever, asthma, or other manifestations of allergy, a possible gastrointestinal allergy was suspected.

Physical examination revealed a poorly nourished man 68.5 inches in height and weighing 121.5 pounds. The temperature and pulse rate were normal. The blood pressure was 94 systolic and 68 diastolic in mm. of mercury. The tongue was smooth, but the

* 2-(N^4-succinylsulfanilamido)-thiazole—sulfasuxadine, Sharp & Dohme.

patient's wife volunteered the information that it had been "beefy red" prior to admission. There was a slight tenderness in both lower abdominal quadrants.

As the initial stool examination revealed the presence of fatty acid crystals, the diagnosis of sprue was immediately considered. However, no fatty acid crystals were found on subsequent daily stool examinations over a period of 12 days. No evidence of parasites was found. Cultures of stools for dysentery bacilli were negative, but the Gregerson modification of the benzidine test for occult blood was positive in all the stools examined. The diet contained meat but was low in fat.

Proctosigmoidoscopic examination revealed normal findings. Roentgen examinations of the chest, stomach, duodenum, and colon also revealed normal findings. However, the interval study of the small intestine disclosed increased caliber of the intestinal loops, clumping of barium, and apparent thickening of the intestinal folds 2 hours after the ingestion of the barium sulfate meal. These findings are characteristic of a deficiency state and not of regional enteritis.

The gastric Ewald test meal examination revealed a free acidity of 30 and a total acidity of 60. The blood count was 4,250,000 red blood cells, with a hemoglobin of 76 per cent, and 3500 white blood cells. The sedimentation rate of the erythrocytes was normal, as were the fasting blood sugar determination, blood Wassermann and Kahn tests, and urinalyses.

Aside from the evidence of the one stool that contained fatty acid crystals, the cause of the diarrhea remained indeterminate. The patient had become symptom free as soon as he had entered the hospital. Throughout the hospitalization period of 12 days he had only one or 2 stools daily. He gained strength, and his weight increased from 121.5 to 126 pounds, even though the residue in the diet had been increased daily.

In view of the patient's response to sulfathiazole therapy 3 years previously, the use of succinylsulfathiazole on an emperic basis was started 6 days prior to his discharge. Two Gm. was given 4 times daily for 3 days, after which 1 Gm. was used 4 times daily during an additional 9 days until a total of 60 Gm. had been taken. While the patient was in the hospital, the fluid intake and output were adequate, the blood sulfathiazole level did not exceed 3.6 mg. per cent, and the urine remained clear.

Second period of observation. Nine days after the patient was discharged from the hospital, Dr. Ledman called by telephone to report that the patient had hemoptysis, massive hematuria, and should be readmitted to the hospital immediately. Upon admission examination of the urine revealed "almost pure blood." The fluid intake and output had been satisfactory, there were no sulfathiazole crystals nor other abnormal findings in the urine, and the blood succinylsulfathiazole level was 2.6 mg. per 100 cc. blood. The use of succinylsulfathiazole had been discontinued 3 days prior to the readmission to the hospital. Stereoroentgenograms of the urinary tract and chest revealed no abnormal findings. Cystoscopic examination and bilateral pyelograms were made by Dr. Charles Higgins and were reported as being normal. The ureteral catheters were left in place for drainage, and blood was observed coming from both kidneys. No tubercle bacilli were isolated from either kidney specimen, and the cultures were negative.

Meanwhile, the prothrombin time of the blood was found to be elevated to 41 seconds using Quick's method (normal 15 seconds).

An injection of 2-methyl-1, 4 naphthaquinone* was given, and transfusion of 500 cc. blood was administered by the slow drip citrate method. Prior to transfusion the red blood cell count was 3,620,000; hematocrit reading 87 per cent of normal (39 cc. per 100 cc. of blood); hemoglobin 75 per cent (11.5 Gm.); volume index 1.21; and color index 1.04. The mean cell diameter was 8.1 microns. The icterus index was 3 units. The

white blood cell count was 3500. Examination of the blood smear revealed a marked macrocytosis, occasional nucleated red cells, 56 per cent neutrophils, 40 per cent lymphocytes, 2 per cent eosinophils, 2 per cent monocytes, and no abnormal white blood cells. The previous finding of free hydrochloric acid in the stomach contents excluded true pernicious anemia.

The blood calcium was reduced to 8.3 and the total blood proteins to 4.9 mg. per cent. The plasma proteins were fractionated by the Tiselius method. Results are summarized in chart 1. The blood urea, carbon dioxide combining power, and cevitamic acid determinations revealed normal findings. All stools were loaded with fatty acid crystals throughout the second hospital observation. Benzidine tests were negative on several of the stools; all the dietary factors remained the same as during the first observation. Therefore, a diagnosis of sprue complicated by a hemorrhagic diathesis was made.

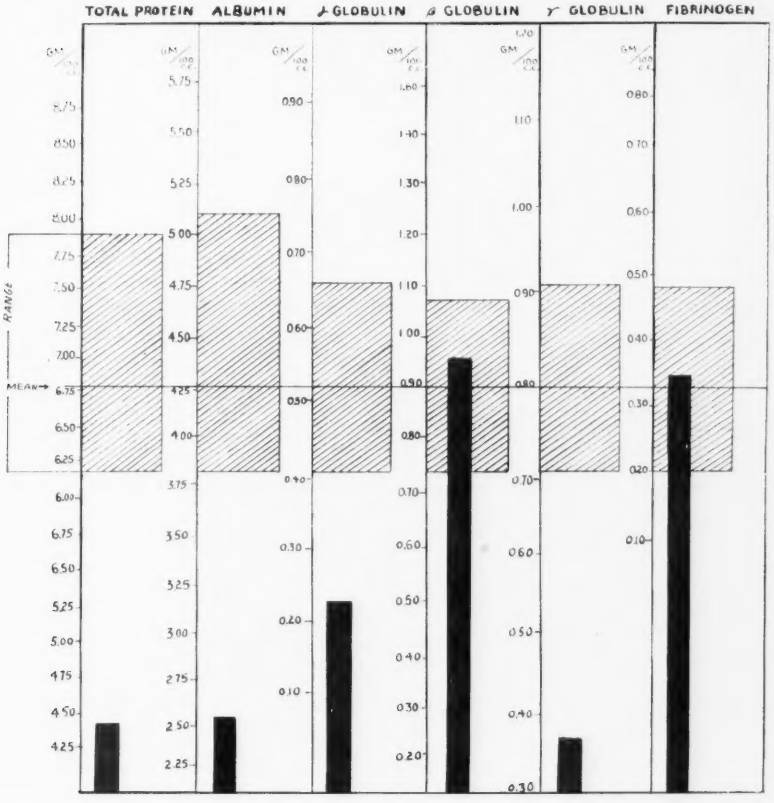

CHART 1

The bromsulfalein and intravenous hippuric acid liver function tests revealed normal findings.

The intravenous use of 2-methyl-1, 4 naphthaquinone* was continued daily for 3 days, after which a similar substance** was given by mouth daily for 26 days. Nine hours after the blood transfusion and first injection of vitamin K substance, less blood appeared in the urine. Three days later the urine was entirely clear, and the prothrombin level of the blood was normal. The hemoptysis had subsided by the time the patient had reached the hospital.

Additional therapeutic measures included the daily intramuscular injection of 3 cc. liver extract (10 units per 3 cc. — Lederle) and 2 cc. vitamin B complex (Beminal Injectable — Ayerst, McKenna) while the patient was in the hospital (16 days). During each of the first 2 days the patient was given 50 cc. of an Amino-Acid Parenteral preparation (Stearns)† in 1000 cc. of 5 per cent glucose solution intravenously, after which a similar type of preparation (Aminoids — Arlington Chemical Co.) was continued orally. Other oral medication included liver extract (Valentine), ketocholanic acids (Ketochol — Searle), a multivitamin preparation (Gelseals Multibebrin — Lilly), and calcium lactate. After the prothrombin time of the blood returned to normal, it remained normal, as did the blood calcium, while the patient was in the hospital. At the end of this time the red blood cell count was 4,110,000; hematocrit reading 89 per cent of normal; hemoglobin 75 per cent; volume index 1.08; color index 0.91; and mean cell diameter of erythrocytes 7.8 microns. After discharge the patient was advised to continue with a high protein, high vitamin, low fat diet; liver intramuscularly twice weekly, and the daily oral use of liver extract, supplemental vitamins, and calcium.

Five months later Dr. Ledman stated that the patient had been working steadily during the previous 4 months. His general health had been good; he had gained 14 pounds in weight and was averaging one formed stool daily. His blood count at that time was 4,300,000 red blood cells with a hemoglobin of 87 per cent, and 5100 white blood cells.

COMMENT

The significant diagnostic features appeared during the second period of observation when the patient was readmitted as an emergency patient with hemoptysis and hematuria, and the diagnosis of sprue was established. The prothrombin time of the blood was elevated to 41 seconds, using Quick's method of determination (normal 15 seconds). The bleeding promptly subsided, and the prothrombin time of the blood returned to normal following a blood transfusion and the intravenous use of 2-methyl-1, 4 naphthaquinone.

Although spontaneous remissions and acute exacerbations occur in sprue, it seems unusual that striking changes should occur within the

*Hykinone (2-methyl-1, 4-naphthohydroquinone-3-sodium-sulfonate, Abbott) A synthetic substance with a vitamin K action in an aqueous, isotonic, injectable solution. One ampule (4 mg.) daily, intravenously.

**Kayquinone (2-methyl-1, 4-naphthoquinone, Abbott) A synthetic substance which has to a high degree the activity of vitamin K extracted from natural sources. One 1 mg. tablet daily.

† Acid hydrolysis of casein fortified with tryptophane.

short period of time between our two periods of observation (9 days). In addition to deficient *absorption* of fat-soluble vitamin K there may have been deficient *synthesis* of this vitamin as a result of the use of succinylsulfathiazole. Our experience confirms that of Poth[1,2] in that during the use of adequate doses of this drug B. coli counts in cultures of the stools diminish to zero. Quick[3] states, "Of great interest and importance was the discovery that vitamin K is synthesized by various bacteria." He refers to the extensive work of Almquist[4] and his coworkers. It was found that B. coli and other common bacteria readily synthesized products which had high vitamin K activity. Uvnäs[5] points out that a K-avitaminosis is easily produced in chickens and birds but with difficulty in mammals, perhaps owing to the synthesis of vitamin K by intestinal bacteria in mammals.

Basic considerations in sprue relate to a chronic deficiency state, particularly to deficient absorption of fat-soluble substances and the erythrocyte-maturing factor. Hanes[6] states that "In the sprue patient fats are normally split, since the pancreatic secretion is maintained, but so poorly absorbed that they are excreted in two or three times the normal amount." Haden[7] emphasizes the close relationship of sprue to pernicious anemia and states that "The bone marrow lacks the erythrocyte-maturing factor, not from a defect in formation as in pernicious anemia, but from a defect in absorption." Quick mentions, "The hypoprothrombinemia in sprue is not surprising; one would expect a hypovitaminosis of all the fat soluble members A, D, K, and possibly E whenever a severe persistent steatorrhea is encountered." Albright and Stewart[8] have reported intensive studies in a case of chronic regional ileitis with proven severe hypovitaminosis of all fat-soluble vitamins, including K, due to steatorrhea. In recent years increasing attention has been given to the lack of absorption of vitamin K in the absence of jaundice in various intestinal conditions. Important contributions to this subject have been made by Butt, Snell, and Osterberg,[9] Snell,[10] and Mackie, Eddy, and Mills.[11]

The difficulties which may be encountered in making a diagnosis of sprue in nontropical regions are emphasized by Ingelfinger.[12] Typically, the patient with sprue has frequent bowel movements consisting of soft, light yellow, frothy and greasy fecal material. Actually none of his 4 reported patients consistently had stools fitting this description, and this experience is illustrated in the present case report. Two of his patients had a hemorrhagic diathesis, and the chief complaint of one patient was hematuria. Obviously, if the diagnosis is not correctly made, the patient may die of internal and external hemorrhages.

Classic features of sprue may be absent or may be obscured by the

secondary nutritional disturbances of the disease. In the early stages of sprue there is a moderate hypochromic anemia, while in the fully developed disease in adults the blood picture very closely resembles that of pernicious anemia. In the present case the blood picture changed from a moderate hypochromic anemia to a macrocytic hyperchromic anemia in a short period of 9 days.

Barker[11] points out that many victims of chronic dysentery may develop a secondary sprue, and this may have occurred in the reported case. Sulfathiazole therapy apparently had induced a remission lasting 3 years.

SUMMARY

A case of sprue complicated by a hemorrhagic diathesis is reported. Although the basic factors in this condition are well known, such as deficient absorption of fat-soluble substances and the erythrocyte-maturing factor, in this case there may have been the additional factor of deficient synthesis of vitamin K. This vitamin is synthesized in the intestinal tract of mammals by the same bacteria that are eliminated by adequate dosage of certain sulfonamides.

The importance of recognizing hypoprothrombinemia in any case of steatorrhea is illustrated. The parenteral use of a vitamin K substance and a blood transfusion resulted in prompt subsidence of the bleeding in this case.

Sprue should be considered in any patient having diarrhea, even in the absence of stools characteristic of this condition during any one period of examination. Secondary nutritional disturbances may obscure the classic features of the disease.

This patient may have developed sprue secondary to bacillary dysentery.

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INFANTILISM, CONGENITAL WEBBED NECK AND CUBITUS VALGUS (TURNER'S SYNDROME)

R. W. SCHNEIDER, M.D. and E. PERRY McCULLAGH, M.D.

In 1938 Turner[1] described a syndrome in women characterized by shortness of stature, sexual infantilism, congenital webbing of the neck, and cubitus valgus. None of the patients had menstruated. All had attained a height ranging from 50 inches to 56 inches. Other congenital defects were commonly associated; 2 of the original 7 cases had ocular muscle palsies. All showed evidence of severe prepuberal hypovarianism, which the author implied was entirely congenital. No hormone assays were obtained in his original cases. In 1942 Varney, Kenyon and Koch[2] reported the association of short stature and primary ovarian insufficiency with an excess of urinary gonadotropins; webbed neck and cubitus valgus were not related findings. They suggested that this be called "ovarian dwarfism." In addition, Albright, Smith and Fraser[3] demonstrated excess urinary gonadotropins in cases having the features originally described by Turner. In the light of these reports, it is now recognized that certain women of short stature with sexual infantilism differ from pituitary dwarfs in a number of ways, although in the past most of them were improperly classified as having pituitary infantilism. It is the purpose of this paper to report 6 additional cases having the anatomic features of Turner's syndrome and to distinguish between this syndrome and pituitary infantilism.

We believe that the ovarian dwarfism of Varney, Kenyon and Koch is fundamentally the same abnormality as Turner's syndrome. The cases here reported are only those showing pronounced congenital anatomic defects, similar to those reported by Turner. In one case a congenital defect is described which has not been reported previously.

Case 7 is not a case of Turner's syndrome. However, the height and congenital webbed neck presented by this patient are characteristic of Turner's syndrome. The case is therefore reported for the sake of comparison and comment.

CASE REPORTS

Case 1—A woman, aged 39, was seen on July 6, 1943, complaining of gastrointestinal distress. Her facial expression showed mental deficiency. She had never menstruated; her breasts were infantile, the nipples small and unpigmented. Axillary and pubic hair approximated ¼ of the normal amounts. An increased carrying angle of the arms, or cubitus valgus, was noted. Webbing of the neck, as judged by a short, thick neck

FIGURE 1—Case 1. Illustrates short neck, increased carrying angle, and infantilism.

and a low hairline, was also present. Roentgen ray examination of the cervical spine showed no developmental defect of the cervical vertebrae as seen in Klippel-Feil syndrome. Her height was 54 inches and span 55½ inches. The uterus was infantile, and a vaginal smear showed many deep cells and leukocytes comparable to those seen after castration.

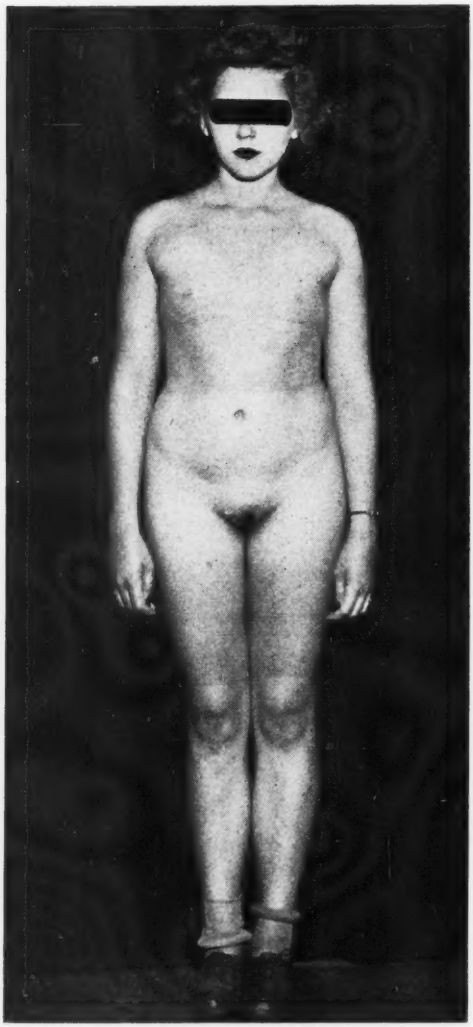

Figure 2—Case 2. Illustrates short neck and infantilism.

Roentgen ray examination of the skull revealed a normal sella turcica. A ketonic fraction showed an excretion of 2.1 mg. of 17-ketosteroids in a 24 hour urine specimen. Gonadotropins were definitely in excess of normal. The average ovarian weight of the test

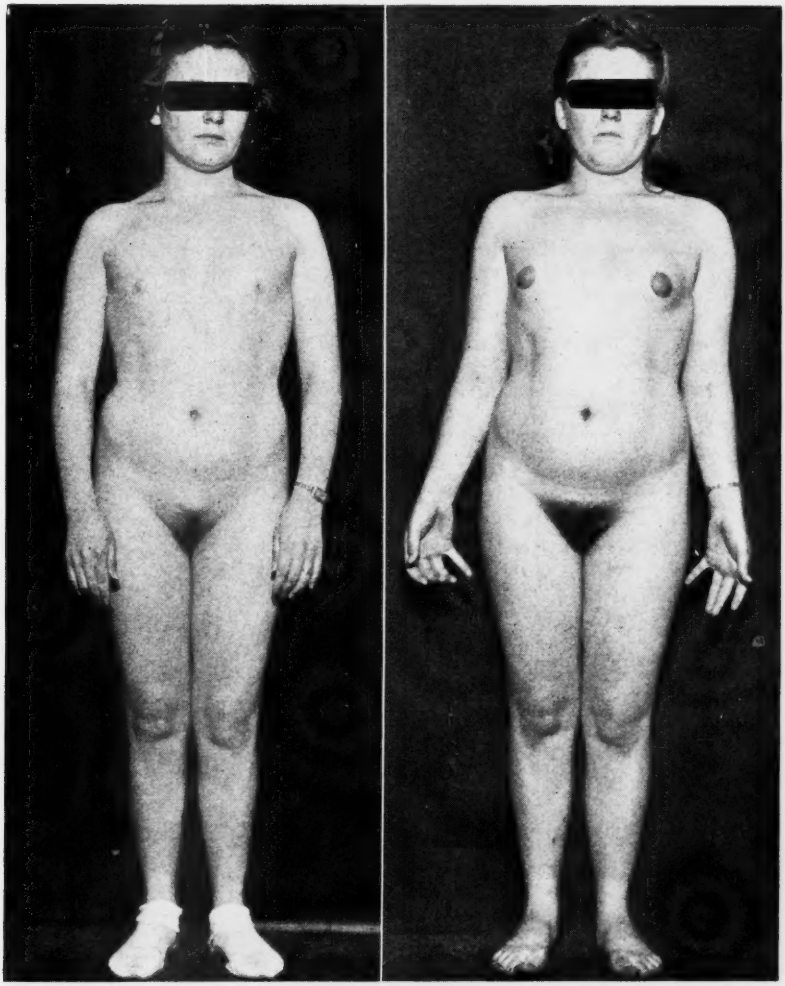

FIGURE 3—Case 3. Before and after 10 months of estrogen therapy. Shows breast development and increase in pubic hair growth.

animals was 45 mg. as compared with 19 mg. in the controls; the average uterine weight was 70 mg. as compared with 19 mg. in the controls.

Case 2—A woman, aged 22, was initially examined on July 26, 1943. She had never menstruated, and breast development had not occurred. Poor vision in both eyes had previously been attributed to lack of retinal pigment.

Her height was 62 inches and span 63¾ inches. She had a short neck but no cubitus valgus. No breast tissue was palpable. Axillary hair was about ⅓ normal and pubic hair ¼ normal. The entire genital tract was infantile, and a vaginal smear was of the castrate type.

Other congenital defects were also observed. The fundi showed an extensive lack of retinal pigment, permitting visualization of the underlying choroidal vessels and sclera. Two rhomboidal areas of normal retinal pigment were present, but the irides were normally pigmented. There was no history of albinism in the family. The retinal defect was classified as albinismus posterior, implying that the albinism was limited to the posterior segments of the eyes.

The gum margins of the upper teeth showed considerable asymmetry between the right and left sides. The fifth finger on each hand exhibited a slight flexion contracture at the middle phalangeal joint, and a similar contracture was present on all toes of both feet.

Roentgen ray examination of the skull revealed a normal sella turcica. Bone age was estimated between 15 and 18 years. A ketonic fraction showed an excretion of 1.8 mg. of 17-ketosteroids in a 24 hour urine specimen, and gonadotropins were in excess of normal.

The patient's brother has since been seen and found to be eunuchoid as well.

Case 3—A woman, aged 21, was first observed on October 17, 1942. She had never menstruated and had not grown normally since the time of expected puberty. She had been partially deaf for years. Mental retardation was evident, and she had an obvious impediment in speech. Twelve siblings were considered normal.

Her height was 54 inches and span 55½ inches. The facies was immature, and the upper teeth were crowded. No breast tissue was palpable. Webbing of the neck and cubitus valgus, as previously defined, were present. Axillary hair was scant, and pubic hair was approximately ⅓ normal. The vagina was the length of an index finger. The walls were smooth and atrophic. The cervix was minute, and the fundus of the uterus could not be palpated. A vaginal smear consisted principally of deep cells.

Roentgen ray examination of the sella turcica was normal. Roentgen rays of the long bones indicated an epiphyseal age between 16 and 17 years.

An insulin tolerance test revealed the following findings: Fasting blood sugar was 80 mg. per cent. After an intravenous injection of 1/10 unit of insulin per kilogram of ideal weight, blood sugars determined 20, 30, 45, 60, 90, and 120 minutes later were 49, 43, 62, 71, and 71 mg. per cent respectively. After the last blood specimen had been obtained, 1/100 cc. of 1:1000 solution of adrenalin per kilogram of body weight was administered subcutaneously. Blood sugar determinations 45 and 60 minutes later were 141 mg. per cent.

If pituitary function is normal, blood sugar levels should return to the fasting level within 2 hours, and the response to adrenalin should be prompt and decisive. These results do not, strictly speaking, satisfy all the requirements of a normal test, but are not sufficiently abnormal to suggest pituitary insufficiency.

A ketonic fraction showed an excretion of 2.4 mg. of 17-ketosteroids in a 24 hour urine specimen. Gonadotropins measured after estrogen therapy were not in excess of normal. Ovarian weights in the test animals averaged 21 mg. as compared with 18 mg. in the controls; uterine weights averaged 25 mg. as compared with 21 mg. in the controls. The significance of the estrogen therapy in this respect is not clear, but may be important in view of observations made in case 5.

Menses have appeared regularly during continuation of estrogen and progesterone therapy, and signs of maturity are beginning to appear.

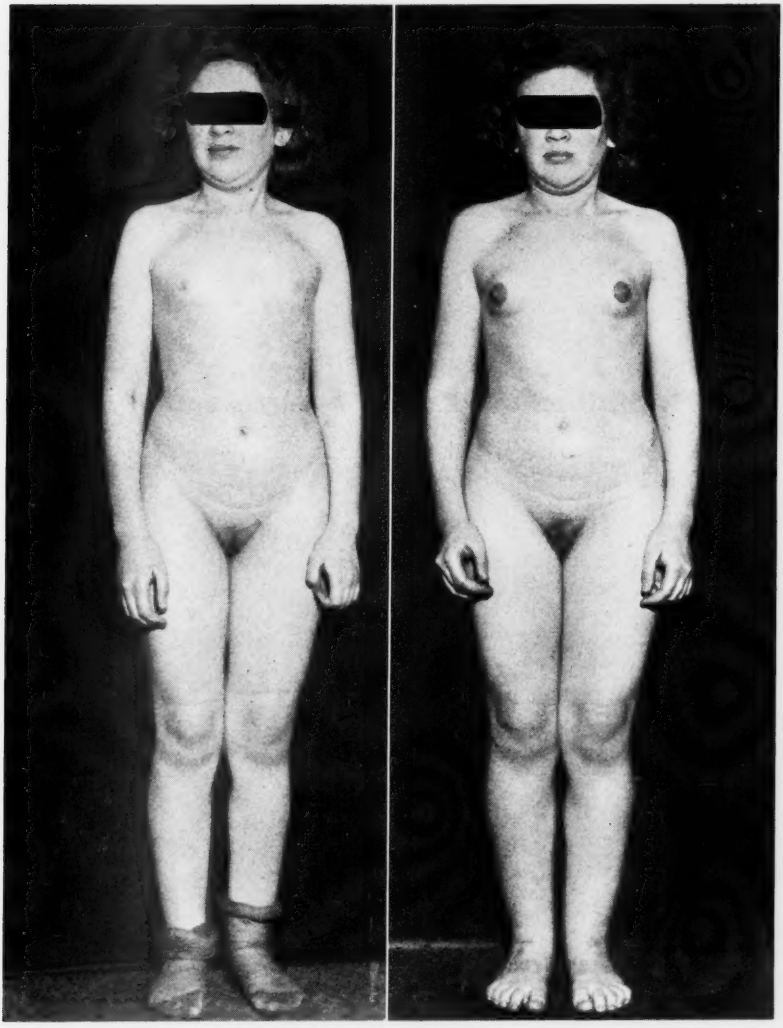

FIGURE 4—Case 4. Shows increase in maturity after 5 months of estrogen therapy.

Case 4—A woman, aged 22, was first examined on March 23, 1942. Her height was 54 inches and span 55½ inches. Menstruation had never occurred. She had had a slight amount of pubic and axillary hair since the age of 12, which at the time of examination approximated ⅓ normal in amount. The breasts and genitalia were infantile.

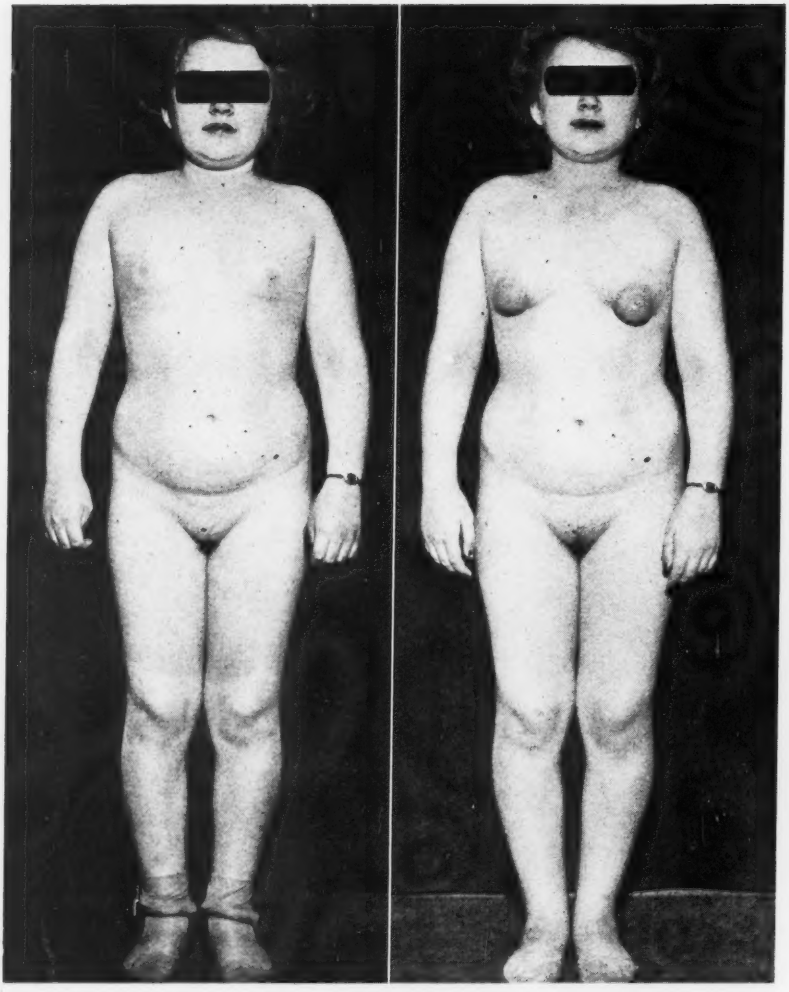

FIGURE 5—Case 5. Before and after estrogen therapy. Interval of 17 months.

The uterus could not be palpated. Webbed neck and cubitus valgus were present. A vaginal smear consisted principally of deep cells and leukocytes. Bone age was retarded about 4 years. A ketonic fraction showed an excretion of 4.2 mg. of 17-ketosteroids in a 24 hour urine specimen. Gonadotropins were definitely in excess of normal. The average ovarian weight of the test animals was 58 mg. and that of the controls 19 mg. Uterine weights of the test animals averaged 68 mg. as compared with 23 mg. in the controls.

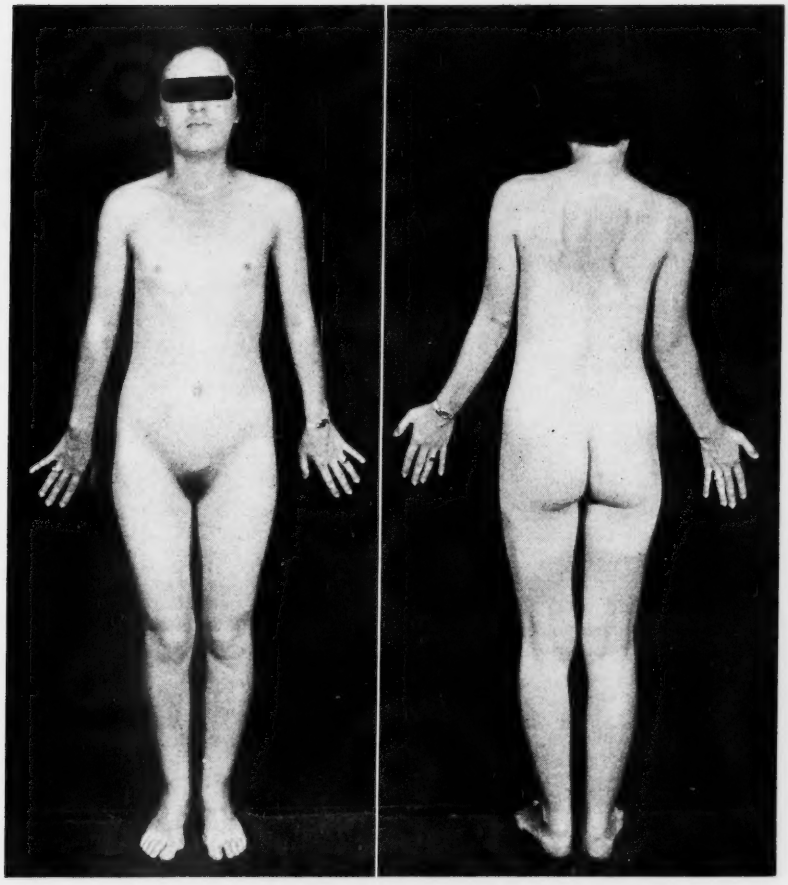

FIGURE 6—Case 6. Shows increased carrying angle, short neck, and sexual infantilism.

The patient has responded satisfactorily to estrogen therapy; bleeding has appeared regularly, and breast development has progressed steadily. Height has not increased after 15 months of continuous therapy, but axillary and pubic hair has increased to approximately ⅔ of normal.

Case 5—A girl, aged 18, was first examined on December 22, 1941 because of primary amenorrhea and lack of continued growth. Her height was 55 inches and span 55½ inches. Three siblings were of normal stature. She presented immature facies, a short neck, and a wide carrying angle. No breast tissue was palpable. Axillary and pubic hair was ½ normal in amount. The vagina, cervix, and uterus were infantile.

Roentgen rays of the sella turcica were normal. Epiphyseal age was estimated at 16

years. A ketonic fraction showed an excretion of 1.3 mg. of 17-ketosteroids in a 24 hour urine specimen; gonadotropins were in excess of normal. Ovarian weights averaged 35 mg. in the test animals and 16 mg. in the controls; uterine weights in the test animals averaged 62 mg. and 18 mg. in the controls. Gonadotropic hormone assay made after institution of estrogen therapy showed no evidence of stimulation, the uterine and ovarian weights of the test animals being the same as those of the controls. This suggests that reduction in excretion of gonadotropins here is comparable with that following estrogen therapy in the postmenopausal period.

Case 6—A girl, aged 16, was first seen on November 4, 1936, complaining of small stature and amenorrhea. There had been no growth in the previous 3 years. Her general health was good. There had been no breast development, and axillary and pubic hair was scant. There had been slight spotting for 3 or 4 days monthly from the age of 13 until the age of 15.

Her height was 57½ inches. The vagina was very small with smooth walls, the cervix was infantile, and the uterus could not be palpated. Basal metabolic rate determinations averaged plus 3 per cent. An oral glucose tolerance test after a single administration of 100 Gm. glucose gave a normal curve as follows:

Hours	Fasting	½	1	2	3	4
mg. per 100 cc. blood	90	155	127	111	80	88

No glycosuria was evident during the test period. Two Friedman tests showed measurable gonadotropic hormone with development of 3 plus mature follicles and a few small hemorrhagic follicles.

Roentgen rays of the left hand and wrist, left elbow, left foot and ankle, left knee, left hip and shoulder at the age of 22 revealed all epiphyses to be closed. Figure 6 reveals the increased carrying angle and low hairline characteristic of this syndrome.

Case 7—A woman, aged 31, complained of pain in the hip joints. Rheumatic fever had appeared at the age of 13 and again at the age of 16 and had been followed by mild aching limited to the hips and knees. Her height was 55 inches, span 58 inches, and distance from top of pubis to sole 28 inches. The weight was 100 pounds, temperature 98 F, pulse 70, blood pressure 158 systolic and 78 diastolic. Menarche had occurred at the age of 15. Menses had appeared regularly about every 28 days, with a flow of 3 or 4 days' duration. Both of two normal pregnancies had been terminated by cesarean section, one in 1936 and the other in 1939.

The patient had a typical webbed neck. The breasts were rather large and full. The pulse was regular in rate, force, and rhythm. There was no precordial shock or thrill. A coarse mitral diastolic murmur was present. Axillary and pubic hair was normal. Vagina and uterus were apparently normal. There was a waddling gait and limitation of motion in both hip joints.

Roentgen rays of the sella turcica were normal, and no abnormality was seen by roentgen ray in the cervical vertebrae. Roentgen rays of the pelvis and hips showed narrowing of both hip joint spaces. There was a slight irregularity of the head of each femur, and fibrocystic changes were present in the adjacent bone. The changes were uniform on both sides. The roentgen diagnosis of the hip-joint disease was osteochondritis.

A ketonic fraction showed 2.6 mg. of 17-ketosteroids in a 24 hour urine specimen.

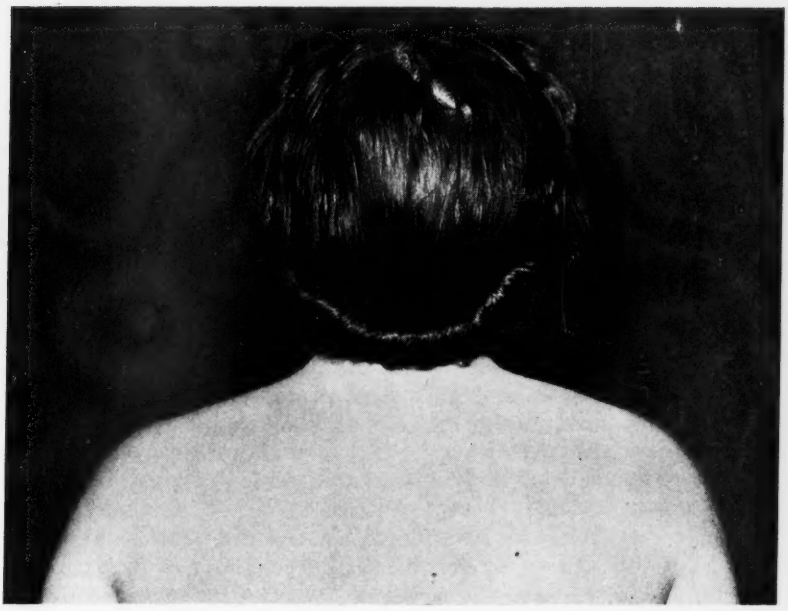

FIGURE 7

The average ovarian weight of the test animals was 16.2 mg. as compared with 14.2 mg. in the controls. The average uterine weight of the test animals was 28.3 mg. as compared with 21.9 in the controls.

The major diagnoses in this case were osteochondritis of the hip and rheumatic heart disease. The short stature associated with the webbed neck probably represented a partial Turner's syndrome.

METHODS

Special methods used in this study were assays for excretion of 17-ketosteroids and gonadotropic hormone. In determining 17-ketosteroid excretion, androgens were first extracted by butyl ether by the technic of McCullagh and McLin.[4] Fractionation of 17-ketosteroids was done by the magnesium oxide adsorption method of Baumann and Metzger,[5] and spectrophotometric determination by the method of Holtorff and Koch.[6] Gonadotropic hormone assays were done by the method of McCullagh and Bowman.[7] Normal values for 17-ketosteroid excretion in women by this method have not been definitely established, but preliminary observations suggest that the lower limit of normal will approximate 4 or 5 mg. in 24 hours.

COMMENT

The association of primary amenorrhea, genital hypoplasia, delayed development of secondary sexual characteristics, and short stature has, until recently, been assumed to be of pituitary origin and has been called pituitary infantilism. This implies that both the growth defect and the genital hypoplasia result from pituitary deficiency. Varney et al and Albright et al, however, have presented evidence that in certain instances where short stature and amenorrhea occur together, there is an abundance of urinary gonadotropins implying that the hypovarianism is not due to pituitary deficiency. The implication seems justified since pituitary dwarfs have no measurable urinary gonadotropins as judged by present methods of assay.

Differentiation of Turner's syndrome from pituitary dwarfism is of considerable clinical interest. In Turner's syndrome axillary and pubic hair begins to appear at puberty and eventually approximates ⅓ to ½ of normal in amount. Conversely, pituitary dwarfs have virtually no axillary nor pubic hair. Response to the administration of estrogens in Turner's syndrome is consistently favorable. Breast development is prompt, cyclic bleeding occurs, and axillary and pubic hair growth increases. This is clearly demonstrated in the cases presented. According to Albright, such a response is absent following estrogen therapy in pituitary dwarfism. In our cases of pituitary dwarfism lack of response to the administration of estrogens has not been conclusive, although the response does not compare with that seen in cases having the features of Turner's syndrome. The proper classification of these cases prior to the administration of estrogen therapy offers some advantage.

Although shortness of stature is common to both conditions, certain features in the growth rate are dissimilar. In hypopituitarism retardation of growth is evident at a very early age, while in Turner's syndrome growth usually progresses normally until the time of expected puberty. Since puberty does not appear, acceleration of growth rate which normally follows puberty does not occur. Consequently, dwarfism is more extreme in hypopituitarism because of earlier retardation of growth rate. In Turner's syndrome height usually reaches 50 to 58 inches, which is decidedly greater stature than is usual in pituitary dwarfism. In Turner's syndrome the women are strong and well nourished; pituitary dwarfs are frail and malnourished.

Congenital defects in addition to webbed neck and cubitus valgus commonly occur in Turner's syndrome, but not in hypopituitarism. Webbed neck occurs without roentgen ray evidence of anomalies in the cervical vertebrae and, as Turner pointed out in his original presenta-

tion, is thus different from the webbed neck of Klippel-Feil syndrome. Turner observed ocular muscle palsies in 2 of his original cases. Albright described coarctation of the aorta and mental deficiency. In the present series 2 patients were mentally deficient, and one of these had nerve deafness. Another patient presented albinismus posterior, failure of development of retinal pigment in both eyes, without a comparable defect in the iris. Coarctation of the aorta was not observed in any of this series.

Precocious senility, amenorrhea, and mammary and genital hypoplasia occur in both syndromes. In each the bone age is delayed, but more so in hypopituitarism than in Turner's syndrome. In the former the epiphyses may never unite, while in the latter they apparently always unite.

These two conditions are further differentiated by assays of urinary 17-ketosteroids and gonadotropins. In pituitary dwarfism urinary gonadotropins are not measurable, and 17-ketosteroid excretion varies from 0 to 1.5 mg. in 24 hours (Albright). However, in Turner's syndrome there is an excess of gonadotropins in the urine; 17-ketosteroid excretion is low, but higher than in hypopituitarism (table 1).

TABLE 1

	Turner's syndrome	**Pituitary dwarfism**
Height	52 to 58 inches:	Less than 48 inches
Endurance	Good	Poor
Nutrition	Good	Poor
Axillary and pubic hair	⅓ to ½ normal	Little or none
Response to estrogens	Slow growth	(?)
Genital hypoplasia	Marked	Marked
Amenorrhea	Present	Present
Response to estrogens	Prompt	(?)
Breast development	None	None
Response to estrogens	Growth	(?)
Other congenital defects	Common	None
Precocious senility	May occur	Commonly occurs
Bone age	Usually retarded	Severely retarded
Urinary gonadotropins	Excessive	None by present assays
17-ketosteroids	Less than normal	Little or none

If stunting of growth observed in the syndrome described by Turner is not a pituitary phenomenon, speculation about its possible origin is interesting. Albright et al suggest an adrenal origin since 17-ketosteroid excretion is low. This is consistent with the fact that growth rate is retarded after puberty is expected, at which time 17-ketosteroid excre-

tion normally is observed to rise. Moreover, it has been established that these steroids are capable of stimulating growth. This might explain the retardation of growth rate occurring after puberty in Turner's syndrome. However, the tallest individual in the present series did not have the highest 17-ketosteroid excretion, which might be expected if this were the complete explanation for the growth defect. Albright et al further suggested that normally estrogens stimulate the production of a pituitary hormone, which in turn stimulates the adrenal cortex to liberate androgens and cause growth. If this interpretation is correct, it is easily understood why estrogens have never successfully caused growth in pituitary dwarfs, since the pituitary is incapable of accepting this stimulation. It does not explain, however, the lack of growth in Turner's syndrome following estrogen therapy, unless we assume a lack of responsiveness on the part of the adrenals. We have not observed any change in height in any cases of Turner's syndrome treated with estrogens for as long as 17 months. A rise in 17-ketosteroid excretion following estrogen therapy apparently has not been reported. The common occurrence of congenital anomalies in this syndrome suggests to us that, whatever the mechanism involved may eventually be found to be, the condition including the growth defect is fundamentally congenital.

High urinary gonadotropin excretion is found rather consistently and is comparable with the increase following castration or at the menopause. Excretion of gonadotropins apparently falls following estrogen therapy here as after treatment of the menopause, as has been demonstrated in case 5. One should not assume, however, that ovarian hypoplasia is invariable present in women with short stature and high urinary gonadotropins. Neither is it implied that high urinary gonadotropin titers in women with primary amenorrhea are limited to those with short stature.

It appears to us that case 7 might be termed "partial Turner's syndrome." The congenital webbed neck is typical of the disorder. The height of the patient was definitely within the range seen in this syndrome, even though 1 or 2 inches in height might presumably have been lost through the abnormality of the hip joints. Obviously, there was no ovarian failure of consequence since the patient was the mother of 2 children. The breasts were well developed, and the patient had lactated following parturition. If our supposition is correct, this case is closely related to Turner's syndrome. The short stature presented here may well be related to the low 17-ketosteroid production, but this in turn cannot be the result of ovarian deficiency, since this obviously does not exist.

SUMMARY

Six cases of Turner's syndrome are presented. Their differentiation from pituitary dwarfism and their similarity to ovarian dwarfism are discussed.

Albinismus posterior, an associated congenital defect not previously described, was present in one case.

Case 6 demonstrates our previous recognition of moderate quantities of urinary gonadotropins in dwarfism associated with infantilism.

Urinary gonadotropins returned to low levels after estrogen therapy in one case.

Case 7, which we have termed "partial Turner's syndrome," is presented here because of the essentially normal function of the ovaries. This case offers presumptive evidence that the short stature in this condition is associated with inadequate 17-ketosteroid production.

Note: Since this paper has been written, we have seen an additional case having all the classical clinical features of Turner's syndrome and in addition the association of abnormal hips, which have x-ray features identical with those of Case 7.

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TREATMENT OF CORONARY ARTERY DISEASE*

F. A. LeFEVRE, M.D.

Physicians in general are familiar with the treatment of coronary artery disease; however, a review of the methods and drugs of choice should be of value.

The most common cause of death after 50 years of age is heart disease, primarily coronary artery disease. The severity of symptoms in coronary artery disease depends entirely upon the degree of arteriosclerosis involving the coronary vessels or the aorta. Although extensive arteriosclerosis of the coronary vessels has been demonstrated post mortem without history of cardiac distress, such cases are unusual.

The 5 chief manifestations of coronary artery disease are (1) angina pectoris, (2) coronary thrombosis with infarction of the myocardium, (3) cardiac asthma with paroxysmal cardiac dyspnea, (4) Morgagni-Adams-Stokes syndrome, and (5) congestive myocardial failure. The two latter manifestations are often complications of coronary thrombosis with infarction of the myocardium.

Recent studies of series of cases by Master,[1] Dack and Jaffe,[2] and Rathe[3] indicate that the prognosis of coronary artery disease, particularly myocardial infarction, is more favorable than has been believed. Only 20 per cent of patients die from the initial occlusion within the first month. Approximately 50 per cent survive the first month and live for several years. Thirty per cent recover and resume normal activity. A definite prognosis of angina pectoris is more difficult to make, but patients may live for years and carry on reasonably normal activities. Sir James Mackenzie, the well known English cardiologist, had his first attack of angina pectoris at 49, but lived for another 25 years, during which time he was very active.

ACUTE CORONARY THROMBOSIS

When the diagnosis of acute coronary thrombosis is relatively certain, absolute bedrest should be prescribed for 6 to 8 weeks. Hospitalization for the first 3 to 4 weeks facilitates treatment of complications. Nursing care, which is very important, is greatly simplified in the hospital during the early weeks. However, moving the patient to the hospital if the attack occurs at home may carry undue risk during the early course of the disease.

* Abstract of lecture presented at Mt. Carmel Mercy Hospital, Post-Graduate Day, Detroit, Mich.

Relief of pain is of first importance. Morphine sulfate is probably the most common drug used. The dose is ¼ gr. repeated in 30 minutes if necessary; 1 gr. may be given during a 2 hour period. Pain is relieved much more rapidly by intravenous administration than by subcutaneous. The intravenous dose is 1/6 gr. repeated in 15 minutes if necessary. Dilaudid may be substituted for morphine in dosages of 1/16 or 1/32 gr. and, in our experience, causes less nausea. Papaverine hydrochloride, if available, is probably the initial medication of choice in ½ gr. dosage intravenously. Morphine or dilaudid can be given later as indicated.

Nitroglycerin is contraindicated in acute coronary thrombosis. It tends to lower blood pressure and depress circulation, which may favor progression of a thrombus.

All patients suffering from pain, dyspnea, cyanosis, or restlessness should have the benefit of oxygen. Even in the absence of these symptoms oxygen is excellent therapy during the first 48 hours.

The following drugs may be indicated in the treatment of coronary artery disease, depending upon the signs and symptoms.

Atropine sulfate. Myocardial infarction may lead to reflex vasospasm, in which the vagus nerve is the afferent path of the reflex. Atropine sulfate, 1/150 gr. by mouth twice daily for 3 days, is prescribed.

Glucose. A common complication is nausea, which may be controlled by the intravenous administration of 200 to 300 cc. of a 10 per cent solution given slowly. The dose may be repeated twice daily for several days, if nausea persists. The use of 50 cc. of 50 per cent glucose is of questionable value.

Quinidine sulfate. Quinidine sulfate should be employed routinely whether or not arrhythmia is present. The drug tends to prevent cardiac arrhythmias and fatal irreversible ventricular fibrillation. A dose of 3 gr. may be administered 3 times daily. An initial dose of 3 gr. will determine the presence of any sensitivity. The use of the drug may be continued for 2 to 3 weeks.

Papaverine hydrochloride. Papaverine hydrochloride, a non-habit-forming, opium alkaloid of the benzyl-iso-quinoline group, has recently been substituted for quinidine in the initial treatment of the disease. It seems to be superior to quinidine, is of very low toxicity, and may be given intravenously with a large margin of safety.

Recent studies by Elek and Katz[4] indicate that papaverine hydrochloride is a powerful and lasting coronary vasodilator. The drug is of value in the treatment of angina pectoris and in controlling the fre-

quency of premature beat; it relieves pain following acute coronary occlusion and prevents arrhythmia following acute myocardial infarction. Papaverine hydrochloride has also been used in peripheral vascular embolism, pulmonary embolism, Raynaud's disease, and ureteral spasm.

Larger doses than ordinarily prescribed should be used. Generally, I use 1 gr. 3 times daily.

Digitalis. Digitalis is indicated in (1) congestive cardiac failure, (2) cardiac dilatation with or without failure, (3) persistent tachycardia with a pulse of over 100, and (4) arrhythmia.

Digitalis should be given slowly in the average case, although rapid administration is advisable if the patient is acutely ill with signs of severe congestive cardiac failure. Ordinarily, a patient weighing between 125 and 175 pounds requires 20 to 24 gr. for complete digitalization. The remaining 10 per cent require approximately 30 gr. The dose cannot be calculated before administration, as each patient responds differently to its use. Usually, 1½ gr. is given 3 times daily for 5 days followed by a maintenance dose of 1½ gr. daily. For more rapid digitalization 6 gr. is given every 6 hours for 3 doses, and 1½ gr. every 4 hours until digitalization is effective. Digitalis intravenously is of value in the management of cardiac emergencies resulting from acute coronary thrombosis. The preparation must be used intravenously with great caution.

Aminophylline. The intravenous administration of aminophylline seems to benefit patients suffering from acute coronary thrombosis. The usual dose is 7½ gr. every 8 hours for 2 days. Diluted with 25 cc. of isotonic sodium chloride it is administered at the rate of 5 cc. per minute. Starting the third day 3 gr. of aminophylline 3 times daily is given orally. Theobromine sodium acetate may be substituted in doses of 7½ gr. 3 times daily before meals. The use of oral aminophylline and theobromine is particularly helpful in congestive cardiac failure. This dosage is frequently maintained for 30 to 60 days.

Caffeine sodiobenzoate. This preparation is indicated only when the systolic blood pressure drops below 100 mm. of mercury; 7½ gr. may be given subcutaneously every 2 to 3 hours until the blood pressure rises above 100 mm. of mercury.

Discourmarin ((3,3'—methylene—*bis*—(4-hydroxycoumarin)). A number of observers[8] have used this preparation from sweet clover to prevent arteriothrombosis or embolism. I have used this drug in the treatment of acute coronary thrombosis and believe that it contributes to a more rapid recovery. It is too early, however, to determine its actual

value. The oral administration of dicourmarin prolongs the prothrombin time. The administration is fairly simple, but a method for calculating exact dosage has not been determined. The effect is lasting and the cost within reasonable limits. Dicourmarin is not yet available for general use.

Diet. During the first 2 weeks of bedrest, the patient should be assisted in eating, as excessive movements of the arms, neck, and trunk should be prohibited During the first 24 hours liquids should be administered exclusively; for the next 2 or 3 days the diet should be semisoft and divided into 5 or 6 meals a day. Thereafter, a bland semisolid diet of approximately 1500 to 1800 calories is adequate. Fluid is limited to 1500 cc. daily. If the patient is overweight, a weight reduction program should be instituted. Tobacco should be eliminated if possible. Small amounts of alcohol may be good therapy.

For elimination I prefer to have patients use the bedpan. Obese patients find it less strain to use a commode next to the bed. Adequate assistance is necessary, however. Strong cathartics are not needed. Mineral oil preparations should be used chiefly; a glycerin rectal suppository may be helpful. A bowel movement every 2 days is adequate.

Duration of bedrest. Duration of bedrest is determined by clinical symptoms, such as pain, temperature, blood pressure, and pulse changes. A large severe infarction requires more prolonged bedrest than a very small infarction. Patients with congestive heart failure require even longer periods of rest. Temperature, white blood cell count, and sedimentation rate should be checked regularly. Serial electrocardiograms evaluate the management and help determine the period of bedrest. The patient should not attempt to get up until the temperature, white blood cell count, and sedimentation rate have been normal for at least one week, and if there has been no evidence of failure. Electrocardiographic changes are frequently slow, and the picture may never return to normal.

Treatment of acute coronary thrombosis does not end with carrying the patient through the first few days of the initial attack of pain. When the patient is improved, he should be told the exact nature of his condition so that he may more intelligently follow the program of treatment. A minimum of 6 to 8 weeks' bedrest should be followed by gradually progressive activity for several months. Any physical activity and nervous strain should be avoided. The psychic management is frequently more difficult than the medical management. With proper care and the complete cooperation of the patient, many patients suffering from this disease can resume reasonably normal activity.

Prognosis. Rathe[3] in a series of 274 cases of myocardial infarction reported a poor prognosis was indicated when

"1. A sinus tachycardia of 100 persisted over 5 days.
2. The age of the patient was over 55 years.
3. The systolic blood pressure dropped suddenly and failed to rise again to a level of 100 mm. mercury within 5 days.
4. Unusual fatigue and apprehensiveness were prominent during the early convalescent period.
5. Congestive heart failure developed.
6. The pulse pressure was 20 mm. of mercury or less.
7. The electrocardiogram revealed an anterior infarction or an indeterminate infarction.
8. There was a gallop rhythm present.

"A good prognosis was indicated . . . if (1) the patient was under 55 years of age, (2) the heart rate did not reach 100 or if it dropped within two or three days to 90 or less, (3) the blood pressure returned to a near normal level, (4) the heart was not enlarged and (5) there were no signs of cardiac insufficiency."

ANGINA PECTORIS

The treatment of angina pectoris involves the treatment of the attack itself and the prevention of an attack. An attack is usually self-limited and very seldom exceeds 15 or 30 minutes, even without medication.

At the onset of an attack the patient should have immediate and complete rest. Attacks are usually shortened by rest in the sitting or standing position rather than the supine position. Deep breathing is often helpful.

Medication, however, is indicated to relieve the symptoms and shorten the duration of the attack. Patients should carry some form of medication that can be used immediately. The most satisfactory drug is nitroglycerin; 1/100 or 1/200 gr. is necessary to relieve an attack. The smallest effective dose can be determined only by trial. Nitroglycerin under the tongue is usually effective within 15 to 30 seconds, although relief may last no longer than 30 minutes. The drug may be used as frequently as necessary and, as a rule, is without harmful effects.

Amyl nitrite by inhalation provides similar relief, but is more difficult to use and is not superior to nitroglycerin.

Prevention of attacks. Strenuous effort, sudden excitement, overeating, excessive use of tobacco, exposure to intense heat and cold, and/or excessive nervous strain tend to promote the frequency of attacks of angina pectoris. Patients soon learn their own limitations and factors which predispose to pain. The avoidance of precipitating factors is a very important part of the prevention of attacks. Patients suffering from angina pectoris need physical and mental relaxation; therefore, an ade-

quate period of rest during the day is most important. Rest for 30 minutes before and after the noon meal frequently will limit attacks during the day. It has been noted that patients are greatly benefited by a period of complete bedrest for several weeks after the initial attack of angina pectoris.

Nitrites. Nitroglycerin may be taken regularly even in the absence of attacks to prevent their occurrence. Sodium nitrite in 3 gr. doses is usually effective in 5 to 10 minutes. The effect lasts longer than that of nitroglycerin and may continue for one to 2 hours. Erythrol tetranitrate in 1½ gr. doses and mannitol hexanitrate in 3 gr. doses usually become effective after 30 minutes. The effect lasts for 4 to 6 hours. The latter drug may prevent attacks but is not as valuable as nitroglycerin in the treatment of an actual attack of angina.

Papaverine hydrochloride. A dose of ½ gr. to 1½ gr. 3 to 4 times daily frequently will reduce the number of attacks. The preparation is non-habit-forming.

Aminophylline. In my experience aminophylline and allied preparations have not been particularly satisfactory in the prevention of attacks of angina pectoris. It may be used alone in a 1½ gr. or 3 gr. dose 3 times daily, or in combination with phenobarbital. A trial of aminophylline or theobromine sodium acetate is well worth while.

Phenobarbital. Frequently, small doses of phenobarbital, ¼ gr. 3 times daily, reduce attacks of angina pectoris to a minimum. Small doses have a mild sedative effect and, no doubt, tend to reduce vasospasm.

Potassium iodide. Routine use of potassium iodide, 15 drops in water once daily after breakfast, helps to control coronary artery disease. It has no specific effect on the prevention of attacks of angina pectoris.

Glandular extracts. The literature reveals that glandular extracts are being used in the treatment of angina pectoris. I have had limited experience with these preparations, and in the few cases in which they have been used no definite benefit has been derived.

Surgical treatment. Subtotal thyroidectomy, cardiopericardiopexy, pectoral anastomosis, cervical thoracic sympathectomy, and paravertebral alcohol injection are surgical forms of treatment. Operation is advised only after careful study and then only when more conservative measures have failed. Occasionally, persons suffering from polycythemia also have typical angina pectoris. Venesection frequently relieves this particular group of patients.

SUMMARY

Because of the high mortality of coronary artery disease after middle life, the methods of treatment and the selection of drugs are important. With adequate bed rest, diet, nursing care, and proper dosage of indicated drugs the prognosis can be greatly improved.

In the treatment of acute coronary thrombosis papaverine hydrochloride, morphine sulfate, and oxygen may be used for the relief of pain. Other drugs of value are quinidine sulfate, atropine, and digitalis. Aminophylline, caffeine sodiobenzoate, and dicourmarin may be indicated in certain cases. The prognosis may be predicted by the presence or absence of certain physical signs and symptoms.

In angina pectoris consideration must be given to the treatment and prevention of attacks. Nitroglycerin is probably the medication of choice in the treatment of attacks. The nitrites, papaverine hydrochloride, aminophylline, and phenobarbital may be beneficial preventative drugs, combined with the elimination of disturbing environmental and psychic factors. Endocrine or surgical treatment of the disease may be indicated when other measures have been without benefit.

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MESENTERIC THROMBOSIS

Report of a Case

F. L. SHIVELY, Jr., M.D. and R. J. F. RENSHAW, M.D.

Mesenteric thrombosis is usually a dramatic episode. Recently, a case of mesenteric thrombosis was seen in which the course was not sudden and spectacular but slow and progressive. Because of the unusual duration of the disease and the diagnostic problems encountered a report of this case seemed justified.

The pathema of mesenteric thrombosis is an involvement of the superior or inferior mesenteric vessels either by embolism or by thrombosis. Over 70 per cent of the cases are venous in origin, and the superior mesenteric vessels are more frequently involved than the inferior vessels.[1] The following conditions have been described as causes of mesenteric thrombosis: valvular heart lesions, arteriosclerosis and atherosclerosis, aneurysm of the abdominal aorta or superior mesenteric vessels, blood dyscrasias (polycythemia vera and leukemia), abdominal tumors, trauma (blows, great exertion, straining, parturition), septic foci (diverticulitis, ulcerative colitis, and pelvic infections), predisposing factors (surgery of the stomach, appendix, hernia, and pelvis), and finally a small group in which no primary cause can be demonstrated.

Although the incidence of mesenteric thrombosis is greatest between the third and sixth decades, persons of any age may be affected. Cases have been reported in patients as young as 5 and over 80 years of age. Women are more commonly affected than men.

The clinical picture depends upon the stage at which the patient is seen, extent of infarction, and duration of the process. Usually there is an acute condition of the abdomen, but infrequently the onset may be slow as in the reported case. Pain is the outstanding symptom. It is sudden in onset, colicky in nature, and may occur in paroxysms. Nausea and vomiting follow the pain, whereas in acute intestinal obstruction the opposite is usually true. Constipation is more common than diarrhea, although loose watery stools sometimes follow a period of constipation. Dark blood is frequently passed in or with the stool.

Temperature, pulse, and respiration depend upon the rapidity of onset, extent of infarction, and duration of the process. In acute massive infarction the temperature may be normal or subnormal with symptoms of shock. In slowly developing infarction the temperature may be normal or septic. Shock is usually present in proportion to the degree of infarction and rapidity of onset. Either generalized or local-

ized abdominal tenderness is usually associated with rigidity and rebound phenomenon. Jaundice has been reported in a small percentage of cases. During the early stages the erythrocyte count is within normal limits, but the leukocyte count is between 15,000 and 40,000. Leukocytosis is absolute, the polymorphonuclear leukocytes usually being in excess of 85 per cent. Roentgenologic examination contributes little to the diagnosis.

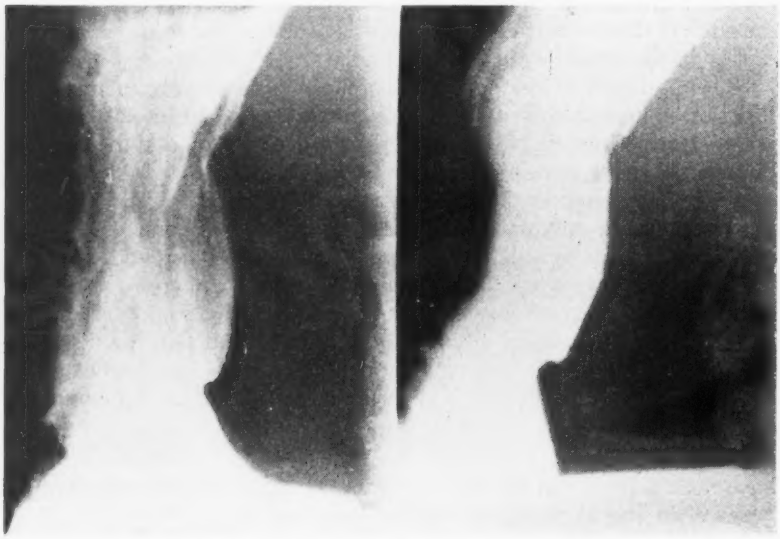

Figure 1

CASE REPORT

A woman, aged 57, was admitted on July 9, 1943 complaining of abdominal pain. The first episode had occurred 13 months prior to admission. The pain was colicky in nature, occurred immediately after meals, and lasted for several hours. Vomiting of frothy material frequently accompanied the pain. There had been no hematemesis nor vomiting of undigested food. Roentgenologic examination of the gastrointestinal tract made elsewhere was reported as being negative. After the initial episode the patient had been relatively free of distress. She had, however, voluntarily for 2 years rigidly restricted her diet and had lost 55 pounds in weight. During the year prior to consultation the patient had subsisted chiefly upon bread and coffee. She especially avoided meat. The appetite had been poor.

Two weeks prior to admission the pain had recurred. The history revealed that she had had two major surgical procedures: A pelvic tumor had been removed in 1907, and a cholecystectomy had been performed in 1931.

The patient did not appear acutely ill. The oral temperature was 98.2 F; pulse 76 beats per minute; systolic blood pressure 115 mm. of mercury and the diastolic pressure 60 mm. of mercury. The skin was dry, unusually wrinkled, and pale, but not icteric. The peripheral blood vessels were sclerotic. Abdominal examination revealed two surgical scars. There was a small postoperative ventral hernia in the lower midline scar. Generalized abdominal tenderness prevented satisfactory or adequate palpation. Rebound tenderness and rigidity, however, were not present. No definite masses nor organs could be palpated. Pelvic examination revealed an atrophic vaginitis. The significance of the postoperative hernia was questioned, because at the first examination it could not be satisfactorily reduced. However, complete reduction at subsequent examinations did not relieve the patient of abdominal distress.

Laboratory examination revealed the following: Urinalysis showed a large number of leukocytes. Hemoglobin estimation was 81 per cent, leukocyte count was 9000. The blood sugar level 3 hours postprandial was 81 mg. per cent. The blood Wassermann and Kahn tests were negative.

A complete gastrointestinal roentgenologic examination showed a gastric ulcer on the upper portion of the lesser curvature. After administration of a barium enema, a lesion found in the sigmoid was interpreted as being inflammatory rather than neoplastic. Roentgenogram of the chest was normal. The tentative diagnosis was gastric ulcer and diverticulosis of the sigmoid colon. The patient was placed on strict ulcer management, antispasmodics, and sedatives.

Sixteen days later on July 28, 1943 the patient was admitted to the hospital as an emergency patient. Since her first visit the abdominal pain had persisted and gradually had become worse. The pain was neither sudden in onset nor had it occurred in paroxysms. For one week prior to admission uncontrollable vomiting had been present. The hospital admitting physician made the following note: "Physical examination revealed a 57 year old woman acutely ill, looking older than her age, dehydrated, and vomiting a dark liquid with a fecal odor." Blood pressure was 140 mm. of mercury systolic and 80 mm. of mercury diastolic. The temperature was 100.8 F, and the pulse 104 beats per minute.

The abdomen was exquisitely tender and rigid but was not board-like. No masses nor organs could be palpated because of the exquisite tenderness. A rectal examination was negative. Laboratory studies revealed a leukocytosis of 16,000. A differential count was not made. The blood urea level was 33 mg. per cent; carbon dioxide combining power 67; blood chlorides 495 mg. per cent; and the blood sugar 169 mg. per cent, apparently several hours after the last intake of food.

The tentative diagnosis was intestinal obstruction with probable perforation of a sigmoidal diverticulum. A Miller-Abbott tube was passed, and parenteral fluid and blood given. Five gm. of sodium sulfadiazine was administered intravenously for 3 consecutive days. On the third hospital day, the patient suddenly became jaundiced, and clay-colored stools were passed. This was attributed to probable sulfadiazine intoxication with hepatitis. The drug was discontinued, and additional blood transfusions and parenteral fluids were administered. The sulfadiazine blood levels rapidly returned to normal; however, the jaundice persisted, and the temperature fluctuated between 98 to 100.5 F.

The subsequent course of the disease raised considerable doubt as to the validity of the diagnosis at hospital admission. The entire clinical picture could not be correlated as one entity. Peritonitis from a ruptured sigmoidal diverticulum did not seem probable because of the increasing leukocytosis with a low grade fever and a soft abdomen. Strict

ulcer management was not continued in the hospital because the pain was not suggestive of peptic ulceration. There was little evidence of a silent common duct stone producing jaundice. A pancreatic malignancy obstructing the common bile duct did not adequately explain the physical and laboratory findings.

Because of conflicting and inconsistent evidence and the presence of persistent deepening jaundice, exploration was advised even though it was realized that the jaundice could have been of a hepatocellular type resulting from sulfadiazine hepatitis.

Exploration of the right upper quadrant was performed on August 13, 1943. Aside from a greatly enlarged yellow-green and swollen liver, the biliary tract was normal. A "T" tube was inserted into the common bile duct and a biopsy of the liver taken. There was no external evidence of peptic ulcer of the stomach. Because of many firm fibrous adhesions and the poor general condition of the patient, further exploration was deemed inadvisable. The patient expired 24 hours postoperatively on the seventeenth hospital day.

By request of the relatives a postmortem examination was limited to the abdomen. The liver presented evidence only of a hepatitis. The stomach was grossly normal, without evidence of peptic ulceration. The entire small and large bowel were gangrenous, and in innumerable areas had undergone lysis. The mucosal continuity of the sigmoid was completely lost for a distance of 10 to 12 cm. The mesenteric arteries and the splenic artery were completely occluded by a severe degree of arteriosclerosis. The abdominal aorta and the left iliac artery were thickened by multiple arteriosclerotic and atheromatous plaques.

The pathologic diagnosis was mesenteric thrombosis secondary to a severe grade of arteriosclerosis involving the aorta and the splenic, iliac, superior and inferior mesenteric arteries.

COMMENT

In retrospect certain points in the history and physical findings are highlighted in view of the pathologic findings. It is purely hypothetical but possible that the initial attack of pain, 13 months prior to consultation, was due to an infarction not large enough to cause the usual spectacular and dramatic phenomena associated with mesenteric thrombosis. During the 13 month interval the arteriosclerotic occluding process was apparently so gradual that symptoms did not occur until massive segments of the gastrointestinal tract had been deprived of sufficient circulation.

Because the arterial occlusion was gradual, the leukocyte count remained normal. We are unable to explain the roentgenologic findings of what appeared to be an ulcerative lesion high on the lesser curvature of the stomach. At the initial fluoroscopic examination the stomach was considered normal, but on the films there appeared to be a shallow ulcer high on the lesser curvature of the stomach (fig. 1). Three days later when the stomach was reexamined roentgenologically by a different examiner, what appeared to be a shallow ulceration was again observed.

The jaundice may have been the result of sulfadiazine intoxication, a toxic manifestation of the extensive degenerative process in the bowel, or a combination of both factors.

Finally, in retrospect, one might ask if treatment should have been different had the true nature of the disease been suspected. We do not believe that mesenteric thrombosis could have been diagnosed or would have been suspected from the initial examination. However, at the time of hospitalization the atypical acute condition of the abdomen might have led to the suspicion, and exploration performed, but in view of the extensive disease no surgical procedure would have been successful. In the treatment of mesenteric thrombosis side-to-side anastomosis is frequently indicated, even though the patient's general condition is poor. On the other hand, exteriorization of the affected segment carries a high mortality rate when parts of the bowel other than the colon are involved.

SUMMARY

A case of mesenteric thrombosis is reported in which the original infarction of the mesenteric vessels presumably occurred 13 months prior to consultation. The differential diagnosis was complicated by the rapid subsidence of the acute condition of the abdomen, by the roentgenologic finding of what appeared to be an ulcerative lesion high on the lesser curvature of the stomach, and by the persistent deepening jaundice.

Postmortem examination revealed the entire small and large bowel to be gangrenous, with innumerable areas having undergone lysis. Continuity of the sigmoid was completely lost for 10 to 12 cm. The mesenteric arteries and the splenic artery were completely occluded by a severe degree of arteriosclerosis.

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EXSTROPHY OF THE BLADDER IN TWINS

CHARLES C. HIGGINS, M.D.

Exstrophy of the bladder, or ectopia vesicae, one of the most unfortunate congenital anomalies, occurs once in approximately 40,000 births, the ratio in the male and female being 7 to 1. A portion of the lower anterior abdominal wall and a portion of the anterior bladder wall are completely lacking, so that the posterior wall, with the trigon, presents itself in the suprapubic region, partially everted, as a result of intra-abdominal pressure. In a review of the literature I have been unable to find a report of the occurrence of this anomaly in twins.

ETIOLOGY

The various theories advanced to explain the etiology fall into 3 groups: (1) mechanical, (2) pathologic, and (3) embryologic.

Von Geldern[1] states that the **mechanical theory** may be divided into: "1. The 'berstungs theorie' (rupture theory), which considers the cause of exstrophy of the bladder and epispadias as a rupture of the anterior wall of the bladder and the adjacent abdominal wall due to a retention of fluids in the bladder. This retention is believed to be due to constrictions at various points along the genito-urinary tract." This implies obstruction of the urethra or the vesical neck producing distention of the bladder, which by direct pressure separates the ends of the pubic bones and recti abdominis. Eventually, the anterior wall of the bladder and the abdominal wall contiguous to it rupture, and healing occurs along the edge of the exposed bladder. The obstructive lesion responsible for the distention of the bladder has never been demonstrated. "2. The mechanical theory, which considers a short or absent umbilical cord as the causative factor. 3. A theory which is not based entirely on a mechanical conception, but depends on a transposition of the embryonal anlagen, and considers that the complicated exstrophies (ectopia cloacae) are due to change in position of the vitelline duct."

The **pathologic** theory advanced by Keith[2] states that toxins from an endometritis, or other forms of infection or irritation, produce a separation of the lateral walls of the caudal portion of the embryo.

Velpeau[3] and Phillips[4] believe that ulceration of the anterior abdominal wall occurs and that this also occurs at the symphysis pubis, with subsequent necrosis and separation. Such ulceration, however, is not recognizable, and necrosis of the ends of the pubic bones has not been observed in postmorten study.

Embryologic theories. Forster[5] contends that arrest in development is the causative factor in the production of simple exstrophy of the bladder and epispadias.

Von Geldern[1] states that "the arrest has affected those parts which had not completed their embryonal development, and that when development recommenced, certain primitive embryonal structures were maintained and developed as such, and those which should have undergone differentiation, had no arrest occurred, failed to make these changes."

Johnston[6] states that any explanation of this anomaly must consider the normal development of the bladder and lower end of the alimentary tract. Complete exstrophy of the bladder complicated by intestinal openings on the extroverted area is caused by rupture of the cloacal membrane. The rupture may occur at any time between the first appearance of the membrane and the subdivision of the cloaca.

Keibel[7] believes that the anomaly may result from a persistent open blastopore.

FIGURE 1

Wyburn[8] concludes: "(5) At any early stage the cloacal membrane is a relatively large area of contact of ectoderm and endoderm extending some distance along the allantoic diverticulum. (6) The allantoic cloacal membrane is later obliterated by the mesoderm pressing in towards the midventral line between the ectoderm and endoderm. (7) Extroversion of the bladder is due to mesodermal deficiency, particularly of the processes of secondary mesoderm arising from the hindend of the primitive streak, following an impaired development of the muscular coat of the bladder, of the symphysis pubis, and the formation of external genitals and the infra-umbilical portion of the anterior abdominal wall. (8) Epispadias is a similar mesodermal error in a minor form."

The following case reports are preliminary observations on the occurrence of exstrophy of the bladder in identical twins.

CASE REPORTS

Twin boys were admitted to the Clinic on June 23, 1943 for surgical correction of exstrophy of the bladder. The boys had been born March 23, 1943, there being one placenta and two cords. M. T. had weighed 5 pounds and 4 ounces at birth, and L. T. had weighed 4 pounds and 12 ounces. Two other children in the family, one girl aged 6 and another aged 5, were normal in all respects. Likewise, there was no evidence of a similar anomaly in the family history.

The children were 3 months old when seen. Their gain in weight had been retarded by frequent stools since birth. M. T. weighed 10 pounds and 12 ounces, and L. T. weighed 8 pounds and 14 ounces.

On physical examination both children appeared malnourished and dehydrated. M. T. had complete exstrophy of the bladder with an associated hypospadias and a bilateral indirect inguinal hernia. The testicles were descended and normal. L. T. likewise had a complete exstrophy of the bladder and associated epispadias. A right indirect inguinal hernia was also present. There was a well healed incision where a left indirect inguinal hernia, which had been strangulated, had been operated upon when the child was 6 weeks of age. The testicles were descended and normal.

The laboratory studies were normal. Complete urologic survey revealed no pathology in addition to the previously mentioned congenital anomalies.

SUMMARY

A preliminary report of identical twins born with exstrophy of the bladder is presented. The occurrence of the anomaly in twins would seem to give credence to the embryologic theory of the development of exstrophy of the bladder rather than to the mechanical and pathologic theories.

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